IV. CLAIMS

What is claimed is:

1. A Inositol 1,4,5-trisphosphate receptor ($InsP_3R$) mutant, comprising at least one substitution of serine with a negatively charged amino acid residue at a phosphorylation site of a wild-type $InsP_3R$, wherein the mutant has an enhanced Ca^{2+} release function as compared to the wild-type $InsP_3R$.

2. The mutant of claim 1, wherein the Ca^{2+} release function is at least 5 times greater than the Ca^{2+} release function of the wild-type $InsP_3R$.

3. The mutant of claim 1, wherein the $InsP_3R$ mutant is an $InsP_3R$-1 mutant and the wild-type $InsP_3R$ is $InsP_3R$-1.

4. The mutant of claim 3, comprising at least one substitution of serine with a negatively charged amino acid residue at a phosphorylation site, wherein the phosphorylation site is selected from residue 1589 or 1755 of a wild–type $InsP_3R$-1 sequence.

5. The mutant of claim 4, wherein the substitution of serine with the negatively charged amino acid is at residue 1589.

6. The mutant of claim 4, wherein glutamate is substituted for serine at residue 1589.

7. The mutant of claim 6, wherein the mutant comprises the amino acid sequence of SEQ ID NO:1.

8. The mutant of claim 6, wherein the mutant comprises the amino acid sequence of SEQ ID NO:1 with one or more conservative amino acid substitutions.

9. The mutant of claim 6, wherein the mutant comprises the amino acid sequence of SEQ ID NO:2.

10. The mutant of claim 6, wherein the mutant comprises the amino acid sequence of SEQ ID NO:2 with one or more conservative amino acid substitutions.

11. The mutant of claim 4, wherein aspartate is substituted for serine at residue 1589.

12. The mutant of claim 11, wherein the mutant comprises the amino acid sequence of SEQ ID NO:3.

13. The mutant of claim 11, wherein the mutant comprises the amino acid sequence of SEQ ID NO:3 with one or more conservative amino acid substitutions.

14. The mutant of claim 11, wherein the mutant comprises the amino acid sequence of SEQ ID NO:4.

15. The mutant of claim 11, wherein the mutant comprises the amino acid sequence of SEQ ID NO:4 with one or more conservative amino acid substitutions.

16. The mutant of claim 4, wherein the substitution of serine with the negatively charged amino acid is at residue 1755.

17. The mutant of claim 16, wherein glutamate is substituted for serine at residue 1755.

18. The mutant of claim 17, wherein the mutant comprises the amino acid sequence of SEQ ID NO:5.

19. The mutant of claim 17, wherein the mutant comprises the amino acid sequence of SEQ ID NO:5 with one or more conservative amino acid substitutions.

20. The mutant of claim 17, wherein the mutant comprises the amino acid sequence of SEQ ID NO:6.

21. The mutant of claim 17, wherein the mutant comprises the amino acid sequence of SEQ ID NO:6 with one or more conservative amino acid substitutions.

22. The mutant of claim 16, wherein aspartate is substituted for serine at residue 1755.

23. The mutant of claim 22, wherein the mutant comprises the amino acid sequence of SEQ ID NO:7.

24. The mutant of claim 22, wherein the mutant comprises the amino acid sequence of SEQ ID NO:7 with one or more conservative amino acid substitutions.

25. The mutant of claim 22, wherein the mutant comprises the amino acid sequence of SEQ ID NO:8.

26. The mutant of claim 22, wherein the mutant comprises the amino acid sequence of SEQ ID NO:8 with one or more conservative amino acid substitutions.

27. The mutant of claim 4, wherein the substitutions of serine with the negatively charged amino acid is at residues 1589 and 1755.

28. The mutant of claim 27, wherein glutamate is substituted for serine at residues 1589 and 1755.

29. The mutant of claim 28, wherein the mutant comprises the amino acid sequence of SEQ ID NO:9.

30. The mutant of claim 28, wherein the mutant comprises the amino acid sequence of SEQ ID NO:9 with one or more conservative amino acid substitutions.

31. The mutant of claim 28, wherein the mutant comprises the amino acid sequence of SEQ ID NO:10.

32. The mutant of claim 28, wherein the mutant comprises the amino acid sequence of SEQ ID NO:10 with one or more conservative amino acid substitutions.

33. The mutant of claim 27, wherein aspartate is substituted for serine at residues 1589 and 1755.

34. The mutant of claim 33, wherein the mutant comprises the amino acid sequence of SEQ ID NO:11.

35. The mutant of claim 33, wherein the mutant comprises the amino acid sequence of SEQ ID NO:11 with one or more conservative amino acid substitutions.

36. The mutant of claim 33, wherein the mutant comprises the amino acid sequence of SEQ ID NO:12.

37. The mutant of claim 33, wherein the mutant comprises the amino acid sequence of SEQ ID NO:12 with one or more conservative amino acid substitutions.

38. The mutant of claim 27, wherein aspartate is substituted for serine at residue 1589 and glutamate is substituted for serine at residue 1755.

39. The mutant of claim 37, wherein the mutant comprises the amino acid sequence of SEQ ID NO:13.

40. The mutant of claim 37, wherein the mutant comprises the amino acid sequence of SEQ ID NO:13 with one or more conservative amino acid substitutions.

41. The mutant of claim 37, wherein the mutant comprises the amino acid sequence of SEQ ID NO:14.

42. The mutant of claim 37, wherein the mutant comprises the amino acid sequence of SEQ ID NO:14 with one or more conservative amino acid substitutions.

43. The mutant of claim 25, wherein glutamate is substituted for serine at residue 1589 and aspartate is substituted for serine at residue 1755.

44. The mutant of claim 43, wherein the mutant comprises the amino acid sequence of SEQ ID NO:15.

45. The mutant of claim 43, wherein the mutant comprises the amino acid sequence of SEQ ID NO:15 with one or more conservative amino acid substitutions.

46. The mutant of claim 43, wherein the mutant comprises the amino acid sequence of SEQ ID NO:16.

47. The mutant of claim 43, wherein the mutant comprises the amino acid sequence of SEQ ID NO:16 with one or more conservative amino acid substitutions.

48. An $InsP_3R$ mutant of an $InsP_3R$ short-form splice variant, comprising a substitution of one or more glycines that form the binding motif of the binding site generated by the splice variation.

49. The mutant of claim 48, wherein the $InsP_3R$ short form splice variant is $InsP_3R$-1 S2-.

50. The mutant of claim 48, further comprising a substitution at residue 1690.

51. The mutant of claim 50, wherein the substitution is a glycine to alanine substitution.

52. The mutant of claim 51, wherein the mutant comprises the amino acid sequence of SEQ ID NO: 23 with one or more conservative amino acid substitutions.

53. A nucleic acid that encodes the mutant of claim 1-52.

54. An expression vector comprising the nucleic acid of claim 53 operable linked to an expression control sequence.

55. A cultured cell comprising the vector of claim 53.

56. The cell of claim 55, wherein the cell is a DT-40 cell.

57. The cell of claim 56, wherein the cell further comprises a nucleic acid that encodes an acetylcholine receptor.

58. The cell of claim 57, wherein the acetylcholine receptor is an M3 receptor.

59. An $InsP_3R$ mutant, comprising at least one substitution of serine with an amino acid with an aliphatic side chain at a phosphorylation site of a wild-type $InsP_3R$, wherein the mutant is nonphosphorylatable.

60. The mutant of claim 55, wherein the nonphosphorylatable mutant is an $InsP_3R$-1 mutant.

61. The mutant of claim 55, wherein the nonphosphorylatable mutant of $InsP_3R$ is selected from the group consisting of an S1755A, or S1589A/S1755A mutation.

62. A nucleic acid that encodes the mutant of claim 55.

63. An expression vector comprising the nucleic acid of claim 62 operable linked to an expression control sequence.

64. A cultured cell comprising the vector of claim 62.

65. The cell of claim 64, wherein the cell is a DT-40 cell.

66. The cell of claim 65 wherein the cell further comprises a nucleic acid that encodes an acetylcholine receptor.

67. The cell of claim 66, wherein the acetylcholine receptor is an M3 receptor.

68. A method of screening for an agent that preferentially modulates Ca^{2+} release by phosphorylated $InsP_3R$, comprising

a. contacting the cell of claim 55 with the agent to be screened, under conditions that allow Ca^{2+} release;

b. measuring Ca^{2+} release; and

c. comparing the amount of Ca^{2+} release in step b with a control cell, wherein the control cell comprises an un-phosphorylated $InsP_3R$ and wherein the control cell is contacted with the agent to be screened, an increase or decrease in Ca^{2+} release as compared to a control cell indicating an agent that preferentially modulates unphosphorylated $InsP_3R$.

69. The method of claim 68, wherein the un-phosphorylated $InsP_3R$ is a nonphosphorylatable mutant $InsP_3R$.

70. The method of claim 69, wherein the nonphosphorylatable mutant comprises a substitution of a serine at a phosphoylation site with an amino acid having an aliphatic side-chain.

71. The method of claim 70, wherein the amino acid having an aliphatic side chain is alanine.

72. The method of claim 70, wherein the phosphorylaytion site is either residue 1589 or1755 or a combination thereof of wild-type $InsP_3R$.

73. A method of expressing a mutant $InsP_3R$ in a cell *in vivo*, comprising

a. providing the expression vector of claim 53;

b. introducing the vector into a cell *in vivo*;

c. maintaining the cell under condition that permit expression of the mutant $InsP_3R$ by the cell.

74. A method of treating a subject with xerostomia, comprising introducing into the subject the expression vector of claim 53 under conditions that an amount of $InsP_3R$ mutant is expressed in an effective amount to alleviate the symptoms of xerostomia.

75. A method of treating a subject with cystic fibrosis, comprising introducing into the subject the expression vector of claim 53 under conditions that an amount of $InsP_3R$ mutant is expressed in an effective amount to alleviate the symptoms of cystic fibrosis.

76. The mutant of claim 1, wherein the $InsP_3R$ mutant is an $InsP_3R$-2 mutant and the wild-type $InsP_3R$ is $InsP_3R$-2.

77. The mutant of claim 76, comprising at least one substitution of serine with a negatively charged amino acid residue at a phosphorylation site, wherein the phosphorylation site is selected from residue 766, 1772, 1856, 2058, 2227 of a wild–type $InsP_3R$-2 sequence.

78. The mutant of claim 77, wherein one or more serines are substituted with glutamate.

79. The mutant of claim 77, wherein one or more serines are substituted with aspartate.

80. The mutant of claim 77, wherein any combination of the serines are substituted with any combination of aspartate or glutamate.

81. The mutant of claim 1, wherein the $InsP_3R$ mutant is an $InsP_3R$-3 mutant and the wild-type $InsP_3R$ is $InsP_3R$-3.

82. The mutant of claim 81, comprising at least one substitution of serine with a negatively charged amino acid residue at a phosphorylation site, wherein the phosphorylation site is selected from residue 934, 1640, 1834, 2009, 2041, 2189 of a wild–type $InsP_3R$-3 sequence.

83. The mutant of claim 82, wherein one or more serines are substituted with glutamate.

84. The mutant of claim 82, wherein one or more serines are substituted with aspartate.

85. The mutant of claim 82, wherein any combination of the serines are substituted with any combination of aspartate or glutamate.

86. A method of inhibiting apoptosis in a transplant in a subject comprising introducing into the transplant the expression vector of claim 53 under conditions that an amount of an $InsP_3R$ mutant is expressed in an effective amount to inhibit cell death.

87. The method of claim 86, wherein the transplant comprises B cells.

88. A method of treating a subject with HIV, comprising introducing into the subject the expression vector of claim 53 under conditions that an amount of $InsP_3R$ mutant is expressed in an effective amount to alleviate the symptoms of HIV.

89. A method of treating a subject with arthritis, comprising introducing into the subject the expression vector of claim 53 under conditions that an amount of $InsP_3R$ mutant is expressed in an effective amount to alleviate the symptoms of arthritis.